Personalized medicine

Bioinformatics Seminar, spring 2017

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1. Definition of personalized medicine
2. Main focus areas
3. Main challenges
4. Personalized medicine in Estonia
What do you think, what is a personalized medicine?
What do you think, what is a personalized medicine?

- Precision medicine
- Stratified medicine
- Targeted therapy

P4 Medicine: Personalized, Predictive, Preventive, Participatory
Personalised medicine refers to prevention, diagnosis and treatment of health disorders, based on individual risk-tailored approach using computational decision support analysis of person’s phenotype and genotype data.

The goal of personalised medicine is to contribute towards preventive, predictive and participatory health system.

Source: Ministry of Social Affairs, 2015
“One-size-fits-all” approach

“Personalized” approach

“The UK is set to become the world leader in ground-breaking genetic research into cancer and rare diseases, which will transform how diseases are diagnosed and treated, thanks to a package of investment worth more than £300 million, the Prime Minister will announce today.”

David Cameron, Prime Minister of UK

1 Aug 2014
“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine – one that delivers the right treatment at the right time.”

Source: http://www.reuters.com/article/us-usa-obama-genomics-idUSKBN0KU06L20150121

Barack Obama, the President of United States, launching “Precision Medicine” initiative

Jan 2015
“It is estimated that more than 500 million DDK have been invested in research infrastructure of relevance to Personalised Medicine in recent years.”

“Estonia has a unique opportunity to be among the leaders of the developers and practitioners of the personalized medicine solutions.”

Source: http://sm.ee/et/uudised/personaalmeditsiin-terviseinnovatsiooni-voimalus-eesti-jaoks (free translation)
Main focus areas
Potential for personalized medicine across disease areas

Potential for “personalized” therapy\(^1\)
(scale of 1-10)

- Oncology
- Immune-related
- Transplant
- CNS
- CV
- Pediatric/pre-natal
- Anti-infectives

Time to realization\(^2\)
(scale of 1-5)

1. Potential based on understanding of disease heterogeneity, clinical relevance of personalized Dx and economic attractiveness

2. Years to realization based on disease understanding, technical feasibility and development timeline for therapeutics

Focus area 1:
Pharmacogenomics (PGx)
Cancer means abnormal cell growth regulation.

The main problem: how to make the drug to distinguish such cells from the others.

Targeted chemotherapy: killing cells that divide rapidly and/or block the cell growth.

The selected therapy is usually based on the nature of the particular cancer cell (has somatic mutations, its DNA is different from patient’s healthy DNA etc.)
The main driver for pharmacogenomics

Percentage of the patient population for which a particular drug is ineffective (in 2001)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Depressants</td>
<td>62 %</td>
</tr>
<tr>
<td>Asthma</td>
<td>60 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57 %</td>
</tr>
<tr>
<td>Arthritis</td>
<td>50 %</td>
</tr>
<tr>
<td>Alzheimer</td>
<td>30 %</td>
</tr>
<tr>
<td>Cancer</td>
<td>25 %</td>
</tr>
</tbody>
</table>

Picture source: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, “Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, Pages 201-204
In 2003, the drug gefitinib was approved for non-small cell lung cancer (NSCLC) by FDA. After few months on the market: for 90% of patients the drug did not work.
Pharmacogenomics - Iressa (gefitinib) story

The drug was effective **only** in patients having certain mutations in **EGFR** gene

FDA reapproved the drug in 2015: a genetic testing is required before using the drug
TASK

1. Read the given text about a specific cancer drug
2. Discuss:
   1. For **what organ type of cancer** the drug is meant for
   2. On what specific **type of that cancer** it works
   3. How the drug works (the general **mechanism**)
Pharmacogenomics - choosing right medication (1)

Used to treat breast cancer if the cancer cell is growing because of the estrogen hormone (it has estrogen receptors) (70%)

This drug **blocks hormone receptors** of the cell, preventing hormones from binding to them.

Approved already in 1972
Pharmacogenomics - choosing right medication (2)

Used to treat **breast cancer** if the cancer cell is overexpressing **HER2 protein** (20%)

More of a protein HER2 (human epidermal growth factor receptor) causes these cells to grow and spread faster than the ones with normal levels of the protein. **Herceptin** binds to **HER2 receptors** and blocks them from receiving growth signals.
Problem: cancer cells are changing their nature even when treated.
Example: 67% of lung cancer tend to become resistant to common cancer medications because of the secondary mutation T790M.
Solution: this drug targets this mutation as well.

Used to treat progressive lung cancer having T790M mutation (Approved by European Commission in February 2016)
Pharmacogenomics - example 4

Used to treat melanoma having BRAFV600E mutation (>50%)

**Protein B-RAF** is part of the pathway that controls cell growth. Mutation BRAFV600E locks this protein into **active state** which leads to **uncontrolled growth of pigment cells**. This drug **blocks** the **mutant B-RAF protein**.
Personalized drug selection/dosage

The right drug and right dosage are selected based on the patient’s genome.

Goal: to avoid taking drug that is not working on that patient or causes adverse side effects.
Personalized drug selection/dosage

Before: one-dose-fits-all approach

After: personalized medicine (from genotype to phenotype)

Genotype

Phenotype

Ultrarapid metabolizers

Extensive metabolizers

Intermediate metabolizers

Poor metabolizers

100 mg

500 mg

100 mg

10 mg

Picture taken from https://www.fda.gov/downloads/ScienceResearch/Special%20Topics/PersonalizedMedicine/UCM372421.pdf
Pharmacogenomics - choosing right medication

NB! Receiving conventional drug doses may lead to life-threatening blood cell production suppression for a patient having nonfunctional TPMT alleles.

Solution: use alternative therapy!

Used to treat lymphoplastic leukemia

Enzyme TPMT is necessary to catalyze this drug from the body.
Pharmacogenomics - adjust the dosage

Warfarin:
Reduces blood clots and thereby reduces the risk of heart attack

The right dosing depends on several genetic variants (CYP2C9, VKORC1):
break it down too quickly and it will not have the desired effect;
too slowly, and the risk of bleeding increases.
Pharmacogenomics - avoid adverse drug effects

Used to treat **HIV**

Side-effect:
causes **life-threatening hypersensitivity reaction**
for patients having
any *57:01 variants*
in immune system gene **HLA-B**
Focus area 2:
Genetic testing related to giving birth
Giving a birth

A couple wants to have a baby

Pregnancy

Birth of the child

Genetic testing:

a) Carrier testing

b) Pre-natal diagnostics

c) Early post-natal testing if there are complications
a) Carrier screening/testing

**Goal:** to test, whether you and your partner both have the **same recessive abnormal gene** (that means: no symptoms) that may result in **affected child**.

**Typically tested diseases:**
Cystic Fibrosis, Sickle Cell Disease, Neurodevelopmental disorders and other Mendelian (one-gene) diseases

Usually done in case there has been the disease in the family tree.
b) Pre-natal testing

**Goal:** To detect genetic problems of the baby before birth.

Typically screening for the **most common chromosomal disorders**: Down syndrome, Edwards syndrome, Patau syndrome, also for rhesus factor conflict

c) Post-natal genetic testing if there are complications

**Goal:** To detect, whether the complications are caused by the *genetic disorder* (and particularly which disorder)

- **Used, if genetic disorder is suspected.**
- **In case** the particular *genetic disorder is found* (not often), then:
  - carrier screening is performed for the parents usually to detect who is the carrier.
    - Often (ca $\frac{2}{3}$ cases) none of them is the carrier. Meaning that the gene mutation was occurred randomly only on the baby (called *de novo mutation*).
Focus area 3:
Prevention and early diagnosis
Cancer screening

- There are lots of gene mutations that are associated with high risk of cancer:
  - Most widely known:
    - some specific mutations in BRCA1 or BRCA2 genes leads to 55-65% risk of developing breast cancer
    - These genes normally produce a protein that assists DNA damage repair
Angelina Jolie

An actress who removed her breasts in 2013 because she carries a BRCA1 mutation and she had lost his mother, grandmother and aunt to cancer.

Picture taken from https://www.pinterest.com/explore/angelina-jolie-mother/
Main challenges
Challenge 1:
How to move from “common medicine” to “personalized medicine”?
TASK 2

1. **Read the given text** - an extraction from personalized medicine strategy of (some) country

2. **What are the 3-4 most important high-level tasks** that need to be done (for launching the national personalized medicine programme)
TASK 3

1. Discuss the tasks with your partner
2. Are the tasks similar?
Challenge 2: Does personalized medicine have any impact?
Targeted cancer treatment is the most promising field, but...

- Most of the “targeted” drugs only block *one of the tumor growing pathways*
- Cancer cells almost always develop a resistance to single-targeted drug
- Most of the drugs are *too toxic* to use in combination
Targeted cancer treatment is the most promising field, but...

IBM Watson Health and Broad Institute Launch Major Research Initiative to Study Why Cancers Become Drug Resistant

$50M research collaboration combines genomic data and IBM Watson to help researchers uncover why tumors become resistant to treatment

10 Nov 2016
Challenge 2: How to organize the massive (and growing) amount of data and knowledge?

Genomic basis of the disease
Influences of disorders of translation and expression
Behavior
Environment
Personalized medicine in Estonia
Personalized medicine in Estonia

Estonian Genome Center

- **Biobank**, holding *biosamples of 5% of Estonian population*
  - Including 2300 full DNA sequences and more
  - + *rich health information* (continuously updated) for all participants

- **Researchers**
- Together with Tartu University Hospital carried out *carrier screening, pre- and post-natal testing* (by now these analyses have moved to separate institution Geneetikakeskus)
Personalized medicine in Estonia

Bioinformatics, Algorithmics and Data Mining Group

Bioinformatics research
(incl multi-omics research)

STACC
Software Technology and Applications Competence Center

Data mining of Electronic Medical Records, Wearables (quantified-self), Decision support systems
Personalized medicine in Estonia

+ collaboration with medical doctors

**Off the Mark**

Let's shut down all his body functions then start them over again...

Why computer engineers should not be surgeons.
Example 1: Decision support system for family doctors

**Patsient Aadu Peedu, mees, 60 a**

- Patsiendi on il tööpõhja diabeet, kuid 23.01.2016 seisuga puudub giükoemia sügavim (HbA1c) mõõtmise viimase aasta jooksul.

- Patsiendi on il tööpõhja diabeet ja tema viimane süstoolse vererühmu vaatetus (23.01.2016: 140.0) >= 135 mmHg, mis on üle normi.

- Patsiendi on il tööpõhja diabeet, kuid 23.01.2016 seisuga puudub mikroalbumüüni mõõtmise viimase aasta jooksul.
Example 2: Quantified-self (wearables)
Take-home message
Take-home message

**Personalized medicine**

is more precise clinical approach by using patient’s genomics (and also other data)

**Main challenge**

Use it in practice; Show that personalized approach has a positive impact

**Ready-to-use focus areas**

Targeted cancer treatment
Pre- and post-natal diagnostics

**In Estonia**

Yes! We do!
Thank you!
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